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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff, v. GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION, Defendants.	C.A. No. 05-160-KAJ

GENENCOR'S AND EDC'S BRIEF IN OPPOSITION TO NOVOZYMES' MOTION FOR PRELIMINARY INJUNCTION

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I. INTRODUCTION AND SUMMARY OF OPPOSITION

Novozymes A/S ("Novozymes") accuses Genencor International, Inc. ("Genencor") and Enzyme Development Corporation ("EDC") of infringing a patent, U.S. Patent No. 6,867,031 ("'031 patent") [Appendix A],[1] which issued almost a year after Genencor first sold SPEZYME® Ethyl. Novozymes does not disclose that the asserted claims were not even submitted to the Patent Office until after Novozymes obtained samples of SPEZYME® Ethyl from Genencor customers around the world, learned from customers that SPEZYME® Ethyl had "higher activity" than Novozymes' competing product (Liquozyme SC), determined the protein sequence of SPEZYME® Ethyl, wrote proposed claims specifically targeted to two amino acid deletions in that protein sequence, and personally met with the patent examiner to persuade her to issue the new claims, all in order to sue Genencor and EDC as soon as the patent issued.

Novozymes' motion for preliminary injunction should be denied because:

- ***SPEZYME® Ethyl does not infringe the asserted claims of the '031 patent because it has less than 95% homology to SEQ ID NO:3.*** Novozymes asserts that Genencor and EDC infringe the '031 patent because SPEZYME® Ethyl has "at least 95% homology" to its alleged "parent," the α-amylase of ATCC deposit 31,195 or SEQ ID NO:3. Novozymes is wrong because the α-amylase of neither ATCC 31,195 nor SEQ ID NO:3 was SPEZYME® Ethyl's parent. Novozymes is wrong because "parent" in the '031 patent must mean "SEQ ID NO:3." Novozymes is wrong because it improperly attempts to limit the calculation of "percent homology" to a single methodology, that of the GAP (GCG) program, contrary to the clear teachings of the '031 specification. Moreover, the GAP (GCG) program calculates percent homology contrary to the teachings of the '031 patent and often generates nonsensical results, as explained in detail below.

- ***Claims 1 and 3 of the '031 patent are invalid and unenforceable over a prior art reference Novozymes inequitably concealed from the Patent Office.*** Novozymes induced the patent

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[1] References to Exhibits in Genencor's and EDC's Appendix in Opposition to Novozymes' Motion for Preliminary Injunction are hereinafter identified as "App. __." Where a specific portion of the exhibit is cited, "App." followed by the relevant page number of the Appendix will appear.

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examiner to grant the '031 patent over the Suzuki and Bisgaard-Frantzen references by presenting experimental data Novozymes claimed was "surprising" and unexpected with respect to the increase in thermostability of α-amylases with the claimed deletion of two amino acids (which, interestingly, Novozymes internally referred to as the "Suzuki double deletion"). Expert testimony demonstrates that there is nothing unexpected about the results. This is itself unsurprising, as Novozymes conducted the experiments in a manner designed to enhance the very effect it claimed to be "surprising." More importantly, the patent examiner did not have the benefit of the Machius reference, which, unlike Suzuki or Bisgaard-Frantzen, provides a rationale for explaining why Novozymes' results were expected and makes claims 1 and 3 of the '031 patent even more obvious. Novozymes knew of Machius (an inventor even submitted a declaration discussing Machius, in detail in a different Novozymes case during prosecution of the '031 patent), yet failed to disclose it to the examiner here. Against the backdrop of Novozymes' panicked reaction to the introduction of SPEZYME® Ethyl, and the very high materiality of the Machius reference, it is clear that Novozymes failed to disclose with deceptive intent, rendering the '031 patent unenforceable.

- ***Novozymes will not be "irreparably" harmed absent an injunction.*** With no likelihood of success, Novozymes is not entitled to any presumption of irreparable harm. Even if it were, that presumption is amply rebutted in this case. Long before the '031 patent issued, Novozymes lost customers and sales because of the superiority of SPEZYME® Ethyl and the high quality service and technical support provided by Genencor and EDC. While Novozymes claims that it is "irreparably harmed" because it has "irreversibly" lost sales and market share, its own declarant testified that those losses were not irreversible. Novozymes also claims that the alleged lost sales and lost market share cause damages which cannot be calculated, yet its own declarant also testified that he and Novozymes colleagues calculated those very damages in "several hours." As this and expert testimony confirms, it is ludicrous to claim that lost profits/sales damages are "incalculable" in a market with only two meaningful players, over a period of a few months.

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- ***Issuing an injunction would harm the public interest and would be unfair to Genencor and EDC.*** Novozymes brought this case because the strong competition presented by SPEZYME® Ethyl caused it to lower prices for its competing product. Not surprisingly, Novozymes plans to raise prices if it obtains an injunction and eliminates competition. Apart from the harm to customers, who even Novozymes concedes do not want to pay higher prices for an inferior product, Novozymes' plan would place unfair burdens on the ultimate consumers of fuel ethanol and those who benefit from cleaner air and a reduction in U.S. petroleum dependency.

Novozymes broke the rules to obtain the '031 patent. It breaks the rules of claim construction to assert infringement. It breaks with reason to assert "irreparable harm" and that an injunction would be equitable. The Court should decline Novozymes' invitation to break with precedent and common sense by issuing an injunction.

II. FACTUAL BACKGROUND

Since its founding in 1982, Genencor has become one of the top 20 biotechnology companies in the United States with $380 million in 2003 revenues.[2] Genencor sells, among other products, enzymes suitable for use in many industries, including food processing, textiles, ethanol production and cleaning products. Genencor's excellent reputation for innovation and corporate citizenship has been repeatedly recognized by trade publications and by popular media. Declaration of Douglas Crabb ("Crabb Decl.") ¶¶ 2 and 3 [App. 1479].

EDC was founded in 1953 and has been serving customers seeking enzymes ever since. EDC distributes enzymes for many different industries, ranging from food processing to textiles. Declaration of Phillip Nelson ("Nelson Decl.") ¶ 2 [App. 1496].

Among the enzymes made by Genencor and distributed by EDC are enzymes suitable for use in fuel ethanol production. One such enzyme is SPEZYME® Ethyl, a *Bacillus stearothermophilus*

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[2] Genencor and EDC present some basic background information here. Facts relevant to specific arguments are discussed in detail within those arguments, as well as in the accompanying declarations.

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α-amylase. SPEZYME® Ethyl is used to help "liquefy" grain meal slurry so that it may be more easily processed into fuel ethanol. SPEZYME® Ethyl liquefies the slurry by breaking down starches, which are composed of long sugar polymers, into smaller molecules, reducing the viscosity of the mash. Crabb Decl. ¶¶ 6, 7 [App. 1480-81] and Nelson Decl. ¶ 3 [App. 1496]. Since sales of SPEZYME® Ethyl began and until very recently, the only competitor to Genencor was Novozymes, through its Liquozyme SC product. Nelson Decl. ¶ 5 [App. 1497] and Declaration of Maurice Beto ("Beto Decl.") ¶ 5 [App. 1514].

Genencor decided to develop a *B. stearothermophilus* α-amylase product (which ultimately became SPEZYME® Ethyl) for the fuel ethanol industry because, among other reasons, Genencor had access to three cloned *B. stearothermophilus* α-amylases that it had acquired from Enzyme BioSystems Ltd. ("EBS"), which exhibited the thermostability and acid-tolerance needed for the fuel ethanol industry. Genencor also believed that it could relatively quickly and easily express the cloned *B. stearothermophilus* α-amylases in economically viable amounts using Genencor's own expression strains. Crabb Decl. ¶ 11 [App. 1482-83]. Ultimately, Genencor decided to further develop an engineered *B. stearothermophilus* α-amylase identified as EBS2 because of its excellent acid-tolerance, thermostability and activity profile. Crabb Decl. ¶¶ 11 and 12 [App. 1482-83].

At the time that Genencor chose to develop EBS2, it believed that sales of this enzyme would not infringe any patent claims owned by Genencor's competitors. In particular, Genencor had evaluated Novozymes' U.S. Patent No. 6,297,038 and determined that SPEZYME® Ethyl did not infringe any of its claims. Further, Genencor believed that the specific double deletion of EBS2 had been taught by Suzuki *et al.* in a 1989 publication, preventing Novozymes or any other competitor from claiming a *B. stearothermophilus* α-amylase with a deletion corresponding to the Suzuki double deletion. Crabb Decl. ¶ 13 [App. 1483-84]. In fact, and as discussed in detail below, Novozymes first began seriously pursuing the claims that issued in the '031 patent only after SPEZYME® Ethyl entered the market.

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III. LAW GOVERNING NOVOZYMES' MOTION FOR PRELIMINARY INJUNCTION

As this Court knows well, a preliminary injunction is a "drastic and extraordinary remedy that is not to be routinely granted." *Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir. 1993). *See also eSpeed, Inc. v. Brokertec USA, LLC*, No. Civ. A. 03-612-KAJ, 2004 WL 62490, at *2 (D. Del. Jan. 14, 2004). Novozymes is entitled to a preliminary injunction only if it shows: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if an injunction is not granted; (3) a balance of hardships tipping in its favor and (4) the injunction's favorable impact on the public interest. *See Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001) (citing *Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1555 (Fed. Cir. 1994)).

Novozymes cannot demonstrate a likelihood of success on the merits unless it establishes that the '031 patent will likely withstand the validity and enforceability challenges set forth below and that it will likely prove that Genencor and EDC infringe the '031 patent. *See Amazon.com*, 239 F.3d at 1350 (citing *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997)); *Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1451 (Fed. Cir. 1988). Novozymes carries a heavy burden to make this showing: "[A]t the preliminary injunction stage, because of the extraordinary nature of the relief, the *patentee* carries the burden of showing the likelihood of success on the merits with respect to the patent's validity, enforceability and infringement." *Nutrition 21 v. U.S.*, 930 F.2d 867, 869 (Fed. Cir. 1991). *See also Reebok*, 32 F.3d at 1555-56. Put another way, if Genencor and EDC raise "a substantial question concerning either infringement or validity, *i.e.*, assert an infringement or invalidity defense that [Novozymes] cannot prove 'lacks substantial merit,'" this Court should not issue a preliminary injunction. *Amazon.com*, 239 F.3d at 1350-51.

As shown below, Novozymes cannot dispel the substantial, if not dispositive, questions about the infringement, validity and enforceability of the '031 patent; nor can Novozymes satisfy the other, equitable factors.

IV. GENENCOR AND EDC DO NOT INFRINGE CLAIMS 1 AND 3 OF THE '031 PATENT BECAUSE SPEZYME® ETHYL DOES NOT HAVE 95% HOMOLOGY TO SEQ ID NO:3

A. Legal Standard For Claim Construction

Determining patent infringement involves two basic steps, properly construing the claims to determine their meaning and scope and comparing the properly construed claims with the accused product to determine if there is infringement. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), *aff'd*, 517 U.S. 372 (1996). The starting point for claim construction is always the words in the claims, which are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art at the time of the invention. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

The ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent. *See Phillips*, 415 F.3d at 1321. Therefore, the claims must be read in view of the patent specification of which they are a part. "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (quoting *Vitronics*, 90 F.3d at 1582). The specification may reveal a special definition given to the claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs. *See id.* at 1316; *Vitronics*, 90 F.3d at 1582.

Courts also review the prosecution history of a patent for evidence regarding the proper construction of claim limitations. *See Phillips*, 415 F.3d at 1317; *Vitronics*, 90 F.3d at 1583-84. The prosecution history can often inform the meaning of claim language by demonstrating how the inventor understood the invention and whether the inventor limited the scope of the claims during the course of prosecution to obtain claim allowance. *See, e.g., Phillips*, 415 F.3d at 1317; *see also Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1579-80 (Fed. Cir. 1996).

Extrinsic evidence, which consists of all evidence external to the patent and its prosecution history, such as dictionaries, treatises and expert testimony, also may be used by the Court to understand the technology of the patent and to explain terms of art. *See Phillips*, 415 F.3d at 1317-18; *Vitronics*, 90

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F.3d at 1582-83. However, extrinsic evidence "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1319. In fact, the Federal Circuit in *Phillips* recently addressed its holding in *Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193 (Fed. Cir. 2002), and found that the *Texas Digital* court improperly restricted the role of the specification in claim construction by suggesting that the specification be consulted "only after a determination is made, whether based on a dictionary, treatise, or other source, as to the ordinary meaning or meanings of the claim term in dispute." *Phillips*, 415 F.3d at 1320.

B. Claim Terms to be Construed

1. "Parent Bacillus stearothermophilus α-amylase"

Novozymes asserts that the "parent" means "a protein having an amino acid sequence without the modification that results in a variant."[3] (PI Mot. 14.) Novozymes consults neither the specification nor the file history to construe the term "parent." Rather, Novozymes relies upon its expert to assert the alleged "ordinary meaning" as confirmed by dictionary definitions. (PI Mot. 13-15.) In view of *Phillips*, Novozymes' construction of "parent," without regard to the '031 patent specification and file history, is incorrect. As detailed below, in contrast, a review of the '031 patent specification and file history establishes that the term "parent" in claim 1 means "SEQ ID NO:3."

a. The examiner relied on SEQ ID NO:3

The '031 patent specification defines the term "parent" but provides several alternative definitions of differing scope. '031 patent, 3:24-42 [App. 8]. The specification most narrowly defines the term "parent α-amylase" as an α-amylase with the amino acid sequence of SEQ ID NO:3.[4] However, the

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[3] For purposes of this motion, Defendants do not dispute Novozymes' construction of the term "variant" as "a protein that has been modified to have one or more changes in its amino acid sequence when compared to a 'parent.'" PI Mot. 14; Declaration of Frances Arnold in Support of Novozymes' Motion for Preliminary Injunction ("Arnold 2005 PI Decl.") ¶ 46; Deposition of Frances Arnold ("Arnold Tr.") 39:18-30, 43:16-17 [App. 1421-22] (defining "variant" as "derived from a parent sequence by [genetic] engineering"). Thus, in claims 1 and 3, "variant" should be construed as "a protein that is derived from a parent by making one or more amino acid substitutions, deletions or insertions in that parent."

[4] The specification lists SEQ ID NOs:1, 2 and 7 as well, but these are not mentioned in or relevant to the claims of the '031 patent.

specification also recites that a "parent" may be an α-amylase that is at least 80% homologous to SEQ ID NO:3 (*i.e.*, may have an amino acid sequence that differs by up to 20% of the amino acids in the sequence) or, even more broadly, an α-amylase that is bound by an antibody that binds to a protein having the amino acid sequence of SEQ ID NO:3 or that is encoded by DNA that hybridizes to DNA encoding the amino acid sequence of SEQ ID NO:3.[5] These broader definitions encompass a wide variety of α-amylases, many of which are only distantly related to SEQ ID NO:3.

When faced with multiple definitions, the Federal Circuit has held that the Court should choose the definition relied upon by the examiner in allowing the claims and avoid those upon which the examiner could not reasonably have relied. *See Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1564-65 (Fed. Cir. 1994). In addition, to better serve the notice function of the claims, the narrower definition is preferred. *Athletic Alternatives*, 73 F.3d at 1581.

In this case, the examiner relied on the narrowest definition for "parent," *i.e.*, that "parent" is a protein having the sequence of SEQ ID NO:3. During prosecution, Novozymes had claims pending which recited that "said parent alpha-amylase has an amino acid sequence which has at least 80% homology to SEQ ID NO:3 and wherein said variant has at least 80% identity to said parent alpha-amylase." Amendment, dated Jan. 14, 2004, at 2 (claim 30) [App. 953]. Further dependent claims increased the identity required between the parent and SEQ ID NO:3 to 95%. In response, the examiner rejected all these claims (including those specifying that the parent has 95% homology to SEQ ID NO:3) as too broad, stating, *inter alia*, that the specification does not enable a variant that is at least 80% identical to a parent that is at least 80% to 95% identical to SEQ ID NO:3. Office Action, dated Apr. 6,

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[5] These last two definitions essentially mean that a small portion of the parent α-amylase is sufficiently similar to a corresponding portion of SEQ ID NO:3 that an antibody can bind to both the parent and a protein of SEQ ID NO:3 or a small piece of DNA can match up (by a physical process called "hybridization") to a small portion of the DNA encoding the parent α-amylase and a corresponding small portion of the DNA encoding the protein of SEQ ID NO:3. The limited disclosure regarding the key structural features of and the lack of examples of variants of SEQ ID NO:3 in the specification would not support claims to variants of this large and diverse set of parents. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963-64 (Fed. Cir. 2002); *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67 (Fed. Cir. 1997).

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2004, at 3-6 [App. 961-64]. According to the examiner, the claims encompassed α-amylase enzymes with an enormous number of variations not enabled by the few examples in the specification.[6] The examiner did indicate that the specification enabled variant α-amylases having at least 90% homology to SEQ ID NO:3. Office Action, dated Apr. 6, 2004, at 4 [App. 962]. The examiner's remarks lead to the conclusion that Novozymes' disclosure in the '031 patent specification does not support defining "parent" as an α-amylase that is 80% identical to SEQ ID NO:3.

Novozymes canceled all claims and added new claims, which issued as claims 1-5 of the '031 patent. Amendment, dated Sept. 6, 2004, at 2 [App. 974].[7] Unlike the previous claims, claim 48 (issued as claim 1) recited a "variant" which has 95% homology to the "parent" without specifying any degree of homology between the parent and SEQ ID NO:3. In allowing these claims, the examiner must have considered the term "parent" to mean SEQ ID NO:3. The examiner's prior rejection had made clear that the broader definitions of "parent" (such as 80% homology to SEQ ID NO:3 and, by implication, the even broader ones as well) were not enabled. She simply would not have allowed such broad claims. Thus, the term "parent" should be construed to mean SEQ ID NO:3, which is both the definition most reasonably relied upon by the examiner in allowing the claims and is the narrowest definition. *See Genentech*, 29 F.3d at 1564; *Athletic Alternatives*, 73 F.3d at 1581.

b. Novozymes' own statements establish that "parent" is SEQ ID NO:3

Novozymes' clear statements in the prosecution history also support the construction of the term "parent" as SEQ ID NO:3. When Novozymes submitted the last set of claims, allowed without change by the examiner, it made statements limiting the term "parent" to SEQ ID NO:3. First, in setting out the support for the new claims, Novozymes cited to the third and fifth paragraphs on page 10 of the specification, which Novozymes characterized in the Amendment as "describing variants of *Bacillus*

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[6] The examiner's rejection was well-founded. *See, e.g., Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213-14 (Fed. Cir. 1991) (holding that claims encompassing thousands of analogs are not supported by disclosure of only a few examples).

[7] Novozymes' motive for hurriedly submitting these new claims is discussed in detail in Section V, *infra*.

stearothermophilus and variants having at least 95% homology to SEQ ID NO:3." Amendment, dated Sept. 6, 2004, at 3 [App. 975]. The passages cited by Novozymes (corresponding to the '031 patent, 7:32-35 and 7:41-51 [App. 10]) refer only to SEQ ID NO:3 and not to any of the broader definitions of "parent." In addition, in asserting that the new claims were enabled by the specification, Novozymes argued:

> The Office concluded that although these [previous] claims are enabled for alpha-amylase variants having 90% homology to SEQ ID NO.3, that [sic] these claims lack enablement for alpha-amylase variants having 80% or 85% homology to SEQ ID NO. 3.
>
> Applicants respectfully submit that this rejection is rendered moot by the new claims as the new claims recite a homology of 95%.

Id. at 3-4 [App. 975-76]. This passage makes clear that Novozymes had changed the scope of the claims to comport with what the examiner would allow – variant α-amylases with 95% homology to SEQ ID NO:3. In yet another passage in the same amendment, Novozymes explicitly stated that "[t]he presently claimed invention is directed to variants of *Bacillus stearothermophilus* alpha-amylase enzymes and to alpha-amylase variants having 95% homology to SEQ ID NO:3." *Id.* at 4 [App. 976].

In these statements, Novozymes asserted that what is now claim 1 is limited to α-amylase variants having 95% identity to SEQ ID NO:3 in order to convince the examiner that the new claims overcame the examiner's rejections of the prior claims. It is axiomatic that Novozymes cannot advance a narrow definition during prosecution to secure claim allowance and then advance a broader definition to encompass alleged infringers. *See, e.g., Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). Novozymes must maintain the same construction for "parent" it used to induce the examiner to allow the claims during prosecution. Novozymes must live with its own definition – "parent" means "an amylase with the amino acid sequence of SEQ ID NO:3."[8]

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[8] When "parent" is construed as SEQ ID NO:3, claims 1 and 3 of the '031 patent are of essentially the same scope. The doctrine of claim differentiation, on which Novozymes will likely rely, does not require a different construction. While claims in a patent are presumed to be of different scope, the doctrine of claim differentiation does not override the construction of claim terms in light of the specification and prosecution history. *See Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1479-80 (Fed. Cir. 1998).

2. "At Least 95% Homology"

Novozymes implicitly construes the term "at least 95% homology" as "sequence identity determined *solely* by the GAP (GCG)[9] computer program." (PI Mot. 15, 20-21, 25-26.)[10] Based upon a reading of the '031 patent specification as a whole, one of ordinary skill in the art of protein engineering could have chosen from many programs available as of March 29, 1995 to align and determine sequence homology,[11] especially those that take all of the sequence changes into account when determining percent homology. All these "known algorithms," and their implementations in software or hand calculations, may be used to determine "percent homology."

a. Background on amino acid sequence comparisons

By way of background, determining "percent homology" or "percent identity" of two sequences is a two step process.[12] Deposition of John Devereux ("Devereux Tr.") 34:12-35:5 [App. 537-38]; Declaration of Thomas Alber ("Alber Decl.") ¶ 10 [App. 133]. First, the two sequences to be compared must be "aligned" by matching up identical residues in the sequences. Alber Decl. ¶¶ 9-11 [App. 133-34]. If the sequences have only a few differences, the stretches of identical amino acids are easily recognized and this task can be performed by hand, on paper. Devereux Tr. 27:16-28:7, 30:23-31:16

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9 The GAP computer program from the GCG package is referred to herein as "GAP (GCG)" to distinguish it from a different sequence alignment program, also called GAP, written by Dr. Xiaoqui Huang, which is designated "GAP (Huang)". That program is discussed in section 2.b, below.

10 Although Novozymes purports to recognize that the specification does not limit calculation of percent homology to the GAP (GCG) program, that is the only program it uses to determine if SPEZYME® Ethyl infringes claims 1 and 3 or mentions in its papers.

11 March 29, 1995 is the earliest possible filing date to which claims 1 and 3 are entitled. Both claims 1 and 3 recite "SEQ ID NO:3," which was not present in the first Danish priority application, No. 00126/95, filed February 3, 1995 (Deposition of Torben Borchert ("Borchert Tr.") 132:25-133:6 [App. 919-20]; Borchert Dep. Ex. 53 [App. 986-1047]); rather, it first appeared in the second Danish priority application, No. 00336/95, filed March 29, 1995 (Borchert Dep. Ex. 54 [App. 1048-1128]; Borchert Tr. 134:22-23 [App. 921]). *See In re Gosteli*, 872 F.2d 1008, 1010 (Fed. Cir. 1989) ("Under section 119, the claims set forth in a United States application are entitled to the benefit of a foreign priority date if the corresponding foreign application supports the claims in a manner required by section 112, ¶ 1.").

12 The Alber Declaration provides additional detail on determining the percent homology of two sequences. Alber Decl. ¶¶ 10-16 [App. 133-36].

[App. 533-36].[13] However, when the two sequences have greater differences, an algorithm, implemented by a computer program, may be used to align sequences. Devereux Tr. 35:6-17 [App. 538]; Alber Decl. ¶ 13 [App. 134]. In certain cases, "gaps" in the alignment are introduced when, for example, a stretch of the target sequence that is highly identical to the reference sequence is interrupted by a region of sequence for which there is no corresponding region in the reference sequence, or there is a stretch of amino acids at the end of one of the sequences without corresponding amino acids in the other sequence.[14] *See example* in Alber Decl. ¶ 11 [App. 134]. After the two sequences are aligned, then the percentage of identical amino acids in the alignment, or the "percent identity" (or, as used in the claims, "percent homology"), can be calculated. Alber Decl. ¶ 10 [App. 133].

b. The '031 specification

As Novozymes points out in its motion (PI Mot. 15), the '031 patent specification does recite a definition of "X % homologous to another amino acid sequence":

> An amino acid sequence is considered to be X % homologous to the parent α-amylase, if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in Science 227 (1985) p. 1435, reveals an identity of X %. The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, *i.e.*, 575 Science Drive, Madison, Wis., USA 53711].

'031 patent 4:36-45 [App. 8]. This passage states that sequence alignment can be performed "via known algorithms," and lists the Lipman and Pearson reference and the GAP (GCG) program as examples. The passage does not, however, limit the "known algorithms" to that in the Lipman and Pearson article or to the GAP (GCG) program, Alber Decl. ¶ 13 [App. 134],[15] but expressly refers to the article and the

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[13] Novozymes' expert, John Devereux, specifically mentioned that sequences of the size at issue in this case could be compared by hand. *Id.*

[14] Dr. Devereux explained that associated "gap penalties" were "hypothetical" numbers, "pulled from outer space." Devereux Tr. 80:13-24 [App. 545].

[15] To the extent "% homology" is construed to require that the calculation be performed by the GAP (GCG) program, the '031 patent is not entitled to any filing date before February 3, 1996, the date of Novozymes' first application referring to the GAP (GCG) program. Novozymes' inventor, Dr. Borchert, testified that he was unable to find reference to the GAP (GCG) program in any of the four Danish priority applications: No. 00126/95 (Borchert Tr. 133:17-24 [App. 920], Borchert

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program as examples ("such as," "may suitably be used"). Devereux Tr. 8:20-25 [App. 527]. In addition, the passage does not define a method for calculating percent identity from the alignment, it merely states that the alignment "reveals" a percent identity. Alber Decl. ¶ 14 [App. 134-35].

By March 29, 1995, there were several different computer programs available for sequence alignment and calculation of percent identity, as well as the possibility of doing both with pencil, paper and a calculator, all of which implement "known algorithms" discussed in the '031 specification. Borchert Tr. 144:17-25 [App. 927]; Devereux Tr. 19:13-18 [App. 528]; Alber Decl. ¶¶ 13-14 [App. 134-35]. For determining "at least 95% homology," the significant difference among these programs (and the "by hand" approach) was whether gaps, either within a sequence alignment or at the end, were counted in determining the percent identity.[16] Prior to March 29, 1995, computer programs, such as the ALIGN and GAP (Huang) programs, were available that did consider the residues in gap regions in calculating percent identity, as were programs, such as the GAP (GCG) program, that did not. Alber Decl. ¶¶ 14, 19-27 [App. 134-38].[17]

(continued...)

Dep. Ex. 53 [App. 986-1047]); No. 00336/95 (Borchert Tr. 135:7-136:13 [App. 922-23], Borchert Dep. Ex. 54 [App. 1048-1128]); No. 01097/95 (Borchert Tr. 138:2-139:4 [App. 924], Borchert Dep. Ex. 55 [App. 1129-1215]); No. 01121/95 (Borchert Tr. 140:6-19 [App. 926], Borchert Dep. Ex. 56 [App. 1216-1303]).

[16] By way of example, the Alber Decl. ¶ 11 [App. 134] provides an example of a sequence alignment, where the "-" indicates deletions as follows:

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FDFPGRGNTYSS
FEFPG--NTY--
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If the deletions are taken into account, the percent identity is equal to the 7 identical residues divided by 12 total residues X 100%, which is 58.3%. If deletions are not taken into account, the percent identity is equal to the 7 identical residues divided by the 8 residues that align with another amino acid X 100%, which is 87.5%, a difference of almost 30%. Alber Decl. ¶ 14 [App. 134-35].

[17] Dr. Alber discusses two programs in detail, Align and GAP (Huang). These programs were available as of March 29, 1995, as evidenced by the Declaration of William Pearson [App. 446-91] (the Align program) (Dr. Pearson is the "Pearson" referred to in col. 4 of the '031 specification) and the Declaration of Xiaoqui Huang [App. 492-524] (the GAP (Huang) program).

The question, thus, is which type of program would the ordinarily skilled artisan have chosen as of March 29, 1995?[18] From the '031 patent specification, those of ordinary skill in the art as of March 29, 1995, would have concluded that a percent identity calculation in the context of protein engineering should consider gaps both within the sequence and at the ends. One reason is because the specification makes clear that deletions should be counted as sequence changes. For example, in defining the sequence changes that generate α-amylase variants, the specification characterizes these changes as including amino acid deletions (which would create a gap in sequence alignment), as well as substitutions and insertions (which would also create a gap). '031 patent 3:59-65 [App. 8]. The specification's nomenclature for describing the sequence changes includes nomenclature for substitutions ("the substitution of alanine for asparagine in position 30 is shown as: Ala 30 Asn or A30N") and for deletions ("a deletion of alanine in the same position is shown as: Ala 30* or A30*"). '031 patent 6:34-64 [App. 9]. According to these definitions, deletions are counted as sequence changes and one ordinarily skilled in the art would have concluded from these passages that deletions or gaps should be taken into account in calculating percent identity. Alber Decl. ¶ 29 [App. 139-40].

Moreover, this is the method that a protein engineer of ordinary skill would have used in this context as of March 29, 1995 because it considers all sequence changes. As Dr. Alber explains, while there are instances in which scientists would not take deletions into account when calculating percent identity, in the context of engineering proteins as in the '031 patent scientists take all of the residues in the two proteins being compared into account. Alber Decl. ¶¶ 44-45 [App. 145].[19] Novozymes' expert, Dr. Arnold, herself testified that a protein engineer would choose algorithms, including whether or not the

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[18] If the court finds that the ordinarily skilled artisan would not, in fact, choose one type of program over another, then the claims are indefinite. As Dr. Alber's declaration illustrates, different programs can give significantly different values for percent identity – in some cases the difference between infringement and non-infringement. Thus, with this interpretation, the claims are invalid. When one cannot tell whether a product infringes or not, claims do not fulfill their notice function and are invalid as indefinite. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003).

[19] *See* Alber Decl. ¶¶ 41-45 for a detailed explanation the genesis of different methodologies for sequence comparison and calculation of percent identity. [App. 143-45].

algorithms consider gaps, depending on what the protein engineer was trying to learn from the sequence comparison. Arnold Tr. 30:17-31:19 [App. 1419-20]. Protein engineers have long considered deletions to be sequence changes and, thus, have considered deleted residues in calculating percent identity. Alber Decl. ¶¶ 46-47 [App. 145-48]. An authoritative treatise on protein sequence comparison, ATLAS OF PROTEIN SEQUENCE AND STRUCTURE, explicitly defined percent identity to include deletions, indicating that "[a] gap was treated as a different amino acid."[20] Likewise, several other references account for gaps when computing the percent identity of two aligned sequences. Alber Decl. ¶ 46 [App. 145-47] and Alber Decl. Exs. 28-30 [App. 354-401]. In contrast, the GAP (GCG) program ignores sequence changes in the form of deletions in an engineered protein and thus overestimates the percent identity when deletions are present. Alber Decl. ¶ 34 [App. 141].

And, Novozymes' proposed limitation of percent homology calculations to solely the use of GAP (GCG) must be wrong, because using GAP (GCG) often leads to puzzling and contradictory results. Two sequences can differ significantly from one another and still be, according to GAP (GCG), 100% identical. Alber Decl. ¶ 37 [App. 142]. For example, GAP (GCG) does not count as a sequence change the deletion of residues 179 and 180 in SEQ ID NO:3, which, according to the '031 patent, increases the thermostability of the α-amylase, and is the essence of the invention claimed in the '031 patent. Alber Decl. ¶ 38 [App. 142]. Similarly, a comparison of the SPEZYME® Ethyl sequence to that of the α-amylase of ATCC deposit 31,195, which differs from the SPEZYME® Ethyl sequence by 5 amino acids, is according to GAP (GCG), 100% identical – a protein engineer would never accept this result. Alber Decl. ¶¶ 38-40 [App. 142-43]; Devereux Tr. 127:20-128:19 [App. 551-52]. In fact, using GAP (GCG), a comparison of just the first 20 amino acids of SEQ ID NO:3 with the entire 514 amino acids of

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[20] Alber Decl. ¶ 46 (citing 5 Dayhoff, ATLAS OF PROTEIN SEQUENCE AND STRUCTURE, National Biomedical Research Foundation, Georgetown University Medical Center, Washington, D.C., D-6 (1972)) [App. 146]; Alber Decl. Ex. 27 [App. 341-53]. Dayhoff actually defined "percent difference," which is the measure of amino acids that differ in an alignment, as compared to "percent identity," which is a measure of the amino acids that are identical in an alignment.

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SEQ ID NO:3 results in a percent identity of 100%! Alber Decl. ¶ 21 [App. 137].[21] The GAP (GCG) program also obviously does not count the amino acids deleted from the end of the SPEZYME® Ethyl sequence as compared to SEQ ID NO:3 even though these deleted amino acids have been shown to significantly impact the thermostability of the protein, the central issue in the '031 patent. Alber Decl. ¶¶ 48-49 [App. 148-49]; Alber Decl. Exs. 34 and 35 [App. 431-438].[22]

These GAP (GCG) results are nonsensical. Thus, as of March 29, 1995, a protein engineer of ordinary skill would have chosen a parent homology calculation method that takes all sequence changes into account to determine whether a variant is at least 95% identical to SEQ ID NO:3, as used in claim 1 and 3 of the '031 patent.

c. Novozymes' (and its expert's) previous litigation position

Finally, even Novozymes own expert, Dr. Arnold, knows that "percent homology" is not and cannot be limited to solely the results of the "percent identity calculations" run on the GAP (GCG) program. When Dr. Arnold was first engaged is this case, she had "percent identity" calculations run on programs other than GAP (GCG); Novozymes' lawyers, not Dr. Arnold, did the work on GAP (GCG). Arnold Tr. 20:6-22:13 [App. 1416-18]. Dr. Arnold also previously submitted a declaration to this Court concerning a related patent with the same specification (claiming different variants of SEQ ID NO:3) in litigation among Novozymes, EDC and Enzyme Bio-Systems Ltd. (later purchased by Genencor).[23] In that declaration, Dr. Arnold provided an explicit definition of "percent homology" in the context of the same specification as the '031 patent specification. For the term "at least 80 % homology to SEQ ID

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21 If "at least 95% homology" is construed to mean only a percent identity as determined by the GAP (GCG) program, then the claims would encompass many, many sequences that differ from SEQ ID NO:3 by large deletions and/or by many deletions but are still "at least 95% homologous" to SEQ ID NO:3. In view of the limited disclosure in the '031 patent regarding what regions of the α-amylase may be deleted and the very few examples, so interpreted, the claims would be so broad as not to be supported by the specification under Section 112, first paragraph. *See Amgen*, 927 F.2d at 1213-14; *Enzo Biochem*, 323 F.3d at 963-64.

22 **REDACTED**.

23 Declaration of Frances Hamilton Arnold, dated January 4, 2002, from *Novozymes A/S v. Enzyme Bio-Systems Ltd. and Enzyme Dev. Corp.*, Civil Action No. 01-804-JJF (NV-0026897-NV-0026924) ("2002 Arnold Decl.") [App. 1425A-Z].

NO:3," Dr. Arnold stated that the maximum number of changes from SEQ ID NO:3 would be 103 additions, substitutions or *deletions* (103 being 20% of the 514 amino acids in SEQ ID NO:3). 2002 Arnold Decl. ¶ 30 [App. 1425L] *cf.* Dr. Alber's manual calculation of percent identity between SPEZYME® Ethyl and SEQ ID NO:3. Alber Decl. ¶ 32 [App. 140].

In contrast to the percent homology calculations put forward in her declaration submitted with Novozymes' current PI motion, Dr. Arnold clearly concluded in her 2002 declaration that deletions should be taken into account in calculating percent identity.[24] Any other construction would render the asserted claims invalid, and ignores the experience and understanding of those skilled in the art.

C. SPEZYME® Ethyl Does Not Infringe Either Claim 1 Or 3

SPEZYME® Ethyl does not infringe claim 1 or claim 3 either literally or under the doctrine of equivalents. Literal infringement is present when each and every element set forth in the patent claims is found in the accused product. *See, e.g., Southwall Techs.*, 54 F.3d at 1575-76. Thus, if the accused product lacks one or more elements of the patent claims, there is no literal infringement. If literal infringement does not exist, the accused product may nonetheless infringe a patent claim under the doctrine of equivalents, which allows a finding of infringement when the accused product is not substantially different from the claimed invention. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997). However, the doctrine of equivalents is limited by prosecution history estoppel, which prevents a patentee from asserting the doctrine of equivalents to recapture subject matter surrendered during prosecution for "a substantial reason related to patentability," including amendments to address rejections under Section 112. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 723 (2002); *Warner-Jenkinson*, 520 U.S. at 33. No range of equivalents is available if a claim element was narrowed during prosecution and the equivalent in question was foreseeable at the time of

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[24] Dr. Arnold testified at her deposition that she does not have any reason to believe her 2002 declaration was inaccurate. Arnold Tr. 101:17-102:19 [App. 1424-25].

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the amendment, within the subject matter that was reasonably surrendered, and directly related to the amendment's rationale. *See Festo*, 535 U.S. at 737.

Applying the appropriate claim construction grounded in the specification, the case for non-infringement is clear. Claim 1 requires, *inter alia*, that the variant have at least 95% homology to the parent *Bacillus stearothermophilus* α-amylase. As explained above, the term "parent *Bacillus stearothermophilus* alpha amylase" should be construed to mean a protein having the amino acid sequence of SEQ ID NO:3. To start with, then, SPEZYME® Ethyl does not infringe because it was not engineered from an α-amylase with the amino acid sequence of SEQ ID NO:3. *See* App. 2275, 2284-85 (Genencor's Interrogatory Responses). In other words, because SEQ ID NO:3 was not the "starting point" for SPEZYME® Ethyl, SPEZYME® Ethyl does not infringe, whatever the "percent homology."[25]

Even if SEQ ID NO:3 were a "parent" to SPEZYME® Ethyl, SPEZYME® Ethyl does not infringe claim 1 or claim 3, which recites that the variant has at least 95% homology to SEQ ID NO:3, because it does not have "at least 95% homology" to SEQ ID NO:3. As also explained above, in view of the '031 patent specification, the percent identity between the amino acid sequence of SPEZYME® Ethyl and the amino acid sequence of SEQ ID NO:3 may be determined by a variety of methodologies, preferably by those that take internal deletions and deletions at the ends into account. Using two computer programs available as of March 29, 1995, Align and GAP (Huang), as well as manual calculation, the percent identity calculated for SPEZYME® Ethyl and SEQ ID NO:3 is 93.2%. (GAP (Huang) reports 93% because it "rounds" to whole numbers). Alber Decl. ¶¶ 22-27, 32 [App. 137-38, 140]. Accordingly, SPEZYME® Ethyl does not have at least 95% homology to SEQ ID NO:3, which is an element of claims 1 and 3. Since SPEZYME® Ethyl does not meet at least one element of both claims 1 and 3, it does not literally infringe claim 1 or 3. *See Southwall Techs.*, 54 F.3d at 1575-76.

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[25] *See* page 1, *supra*; Deposition of Christian Jorgenson ("C. Jorgenson Tr.") 31:4-10 **REDACTED** *Cf.* S. Jorgenson Tr. 75:5-76:16, Ex. 10 [App. 1457-58, 1461-63].

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SPEZYME® Ethyl also does not infringe either claim 1 or 3 under the doctrine of equivalents due to prosecution history estoppel. Novozymes has clearly surrendered any α-amylase variants with less than 95% homology to SEQ ID NO:3. During prosecution, the examiner rejected claims that recited variants that have at least 95% homology to a parent having at least 80% homology to SEQ ID NO:3 and to variants at least 80% homologous to SEQ ID NO:3. Office Action, dated Apr. 6, 2004, at 2-9 [App. 960-67]. In response to these rejections, Novozymes submitted a new set of claims that recited variants that were at least 95% homologous to the "parent" and made clear that "parent" means SEQ ID NO:3. Amendment, dated Sept. 6, 2004, at 2-4 [App. 974-76]. Thus, in making this amendment, Novozymes narrowed this element of the claims creating estoppel for equivalents having less than 95% homology to SEQ ID NO:3. *See Festo*, 535 U.S. at 723. In addition, the narrowing is directly relevant to the equivalent in question here – variants having less than 95% homology to SEQ ID NO:3 – and these variants were certainly foreseeable, as the prior pending claims recited variants with less than 95% homology. Accordingly, no range of equivalents is available to Novozymes for the limitation that the variant have 95% homology to SEQ ID NO:3. *See id.* at 737.[26] SPEZYME® Ethyl, having 93.2% homology to SEQ ID NO:3, does not infringe either claim 1 or 3 under the doctrine of equivalents.

There is, then, at least a substantial question as to infringement of the '031 patent. For this reason alone, Novozymes' motion should be denied.

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[26] In its PI Motion, Novozymes claimed to have identified the "parent" α-amylase of SPEZYME® Ethyl as the α-amylase found in the *Bacillus stearothermophilus* isolate deposited with the American Type Culture Collection (ATCC) as accession number 31,195. (PI Mot. 19.) Novozymes then claims to have "demonstrated" that SPEZYME® Ethyl infringes claim 1 by showing that the amino acid sequence of SPEZYME® Ethyl has at least 95% homology to the sequence of the α-amylase from isolate ATCC 31,195. (PI Mot. 19-20.) This argument is both irrelevant and wrong. It is irrelevant because, as discussed above, the term "parent" is limited to an α-amylase with the amino acid sequence of SEQ ID NO:3. It is wrong because Novozymes offers no proof that SPEZYME® Ethyl was produced by engineering the α-amylase from the ATCC 31,195 isolate (Novozymes' declarants turned out to know *nothing* on this score, despite have sworn to statements on this issue. *See* C. Jorgenson Tr. 26:13-28:14, 28:24-29:2, 29:3-30:23 [App. 1466-70].) In fact, SPEZYME® Ethyl was not derived from the ATCC 31,195 isolate amylase, but instead from a different strain of *Bacillus stearothermophilus*, which had been deposited with the ATCC as accession number 39,709. Genencor Interrogatory Response, No. 2 [App. 2277-80].

V. THE '031 PATENT IS INVALID AND UNENFORCEABLE

The '031 patent should never have issued. The patent examiner properly rejected Novozymes' claim to the "Suzuki double deletion." *See* NV-0004048-50 [App. Ex. Q]. The examiner ultimately accepted claims without the benefit of a critical reference, Machius, which taught even more than Suzuki and Bisgaard-Frantzen, and would have supported an even stronger obviousness rejection no experimental results could overcome. In fact, Novozymes concealed Machius from the '031 patent examiner while simultaneously litigating that reference in another case.

A. Asserted Claims 1 And 3 Of The '031 Patent Are Invalid Because They Were Obvious To One Of Ordinary Skill

1. Legal Standards For Obviousness

In determining whether a claim is invalid as obvious under 35 U.S.C. § 103(a), the court should consider: (1) the scope and content of the prior art (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective indicia of nonobviousness. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372-73 (Fed. Cir. 2005) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). When a finding of obviousness is based on a combination of references, the prior art must provide the motivation to combine. *See Merck*, 395 F.3d at 1375; *Princeton Biochems., Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1338 (Fed. Cir. 2005).

During prosecution, the examiner bears the initial burden of establishing a *prima facie* case of obviousness. *See In re Kumar*, 418 F.3d 1361, 2005 WL 1939792, at *3 (Fed. Cir. Aug. 15, 2005). Once the examiner has done so, the burden shifts to the applicant to rebut the *prima facie* case. *See id.* When rebuttal evidence, such as unexpected results, is provided, the *prima facie* case dissolves, and the decision on obviousness is made anew based on the entirety of the evidence -- both the obviousness and the rebuttal evidence. *See id.*, at *5. Nevertheless, where there is a strong case of obviousness, evidence offered to show unexpected results may be insufficient to overcome the teachings of the prior art. *See In re Eli Lilly & Co.*, 902 F.2d 943, 946-48 (Fed. Cir. 1990) (holding that data offered as showing

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unexpected results did not outweigh the clear teaching of the prior art); *In re Nolan*, 553 F.2d 1261, 1266-67 (C.C.P.A. 1977).

2. Novozymes' Claims Were Rejected As Obvious Over Two References

When Novozymes added claims that issued as claims 1-5 of the '031 patent, it referred to a rejection of a previously pending set of claims "over Suzuki et al. in view of Bisgaard-Frantzen et al. with respect to [now canceled] claims of a similar scope to the draft claims,"[27] and discussed its rebuttal evidence with respect to that prior rejection. In that prior rejection, similar claims[28] were rejected over "Suzuki"[29] and "Bisgaard-Frantzen."[30] Claims 1 and 3 are directed to α-amylases of *B. stearothermophilus* ("BSG") comprising a deletion of amino acids 179 and 180 (using SEQ ID NO:3 for numbering). Such variant α-amylases are referred to herein as "BSGdel."

The examiner relied on Suzuki for its teaching of a mutant *B. amyloliquefaciens* α-amylase ("BAN," referred to in Suzuki as "BAA") with increased thermostability in which amino acid residues 176 and 177 (equivalent to residues 179 and 180 of SEQ ID NO:3 of the '031 patent) had been deleted. Suzuki was a study directed at identifying regions in the amino acid sequence of BAN that are responsible for its low thermostability as compared to the more thermostable α-amylase of *B. licheniformis* ("BLA"). Declaration of Gregory Zeikus ("Zeikus Decl.") ¶ 39 [App. 562]. On the basis of both a comparison of the linear amino acid sequences of BAN and BLA and measurements of the thermostabilities of a number of BAN mutants, Suzuki identified a region, region I, in BAN as particularly important for the enzyme's thermostability. Zeikus Decl. ¶¶ 40-42 [App. 562-63]. A mutant BAN in which two amino acids, Arg-176 and Gly-177, within region I were deleted exhibited a greater thermostability than BAN. Zeikus Decl. ¶ 42 [App. 562-63]. This mutant is referred to herein as "BANdel."

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27 Amendment, dated Sept. 6, 2004, at 3 [App. 975].

28 Office Action, dated July 29, 2003, at 9 [App. 950]; Preliminary Amendment, dated Dec. 19, 2001, at 1 and 2 (claims 33 and 39) [App. 935-36].

29 Suzuki *et al.*, *Amino Acid Residues Stabilizing a Bacillus α-Amylase against Irreversible Thermoinactivation*, 264 J. BIOL. CHEM. 18833 (1989) (Borchert Dep. Ex. 52) [App. 980-85].

30 Bisgaard-Frantzen *et al.*, PCT publication WO95/10603 (Zeikus Decl. Ex. 4) [App. 666-771].

Suzuki merely presented a linear alignment between BAN and BLA, *i.e.*, an alignment between the primary structures of the enzymes, that shows the presence of Arg-176 and Gly-177 in BAN as two additional amino acids relative to BLA. Zeikus Decl. ¶ 43 [App. 563]. In the absence of the availability of an X-ray crystal structure of either BAN or BLA, Suzuki could not explain why deleting Arg-176 and Gly-177 in BAN increased thermostability, but speculated that it might be the result of changes in charge, hydrophobicity or size of amino acid side chains in the mutant BAN enzyme that made it more thermostable than wild type BAN. Zeikus Decl. ¶¶ 41, 44 [App. 562, 563].

Bisgaard-Frantzen was relied on by the examiner for its teaching that BAN, BLA and the α-amylase of *B. stearothermophilus* ("BSG") are homologous such that deletion of residues in BSG corresponding to Arg-176 and Gly-177 of BAN would be expected to have similar effects. Bisgaard-Frantzen was also relied on for a linear alignment of amino acid sequences showing that positions 176 and 177 of BAA correspond to residues 179 and 180 of BSG.[31] Nothing was stated regarding the three-dimensional structures of the three α-amylases.

Based on the combination of these references, the examiner concluded:

> Therefore, it would have been obvious to one of ordinary skill in the art to introduce the mutations disclosed by Suzuki et al. into the corresponding positions of *Bacillus stearothermophilus* α-amylase in order to produce a homologous α-amylase which would have been reasonably expected to have similar improved properties in view of the known homology between these α-amylases.

Office Action, dated July 29, 2003, at 9 [App. 950].

Significantly, Novozymes never even contended that the examiner had failed to establish *prima facie* obviousness. Rather, it chose to rebut obviousness based on allegedly unexpected results that were presented to the Patent Office by way of the Declaration of Torben V. Borchert Under 37 C.F.R. § 1.132, dated Sept. 6, 2004, ("Borchert Declaration") at ¶ 9. Arnold Dep. Ex. 43 [App. 1430].

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[31] Similar teachings are found in Gray, U.S. Patent No. 5,093,257 (issued Mar. 3, 1992). Zeikus Decl. Ex. 18 [App. 888-910].

3. The Alleged Unexpected Results That Led To Withdrawal Of The Obviousness Rejection Were, In Fact, Not Unexpected

Any differences between a claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *See In re Merck & Co.*, 800 F.2d 1091, 1098-99 (Fed. Cir. 1986).

Without defining the expectations of one of ordinary skill in protein engineering as of March 29, 1995, the earliest effective date of the '031 patent (*see* n. 11, *supra*), Novozymes contended that claims 1 and 3 were non-obvious over the prior art on the basis of unexpected results. Amendment, dated Sept. 6, 2004, at 4-5 [App. 976-77]. Specifically, in order to secure allowance of the '031 patent, inventor Torben Borchert and his attorney asserted to the Patent Office that the magnitude of the increase in stability of BSGdel over BSG relative to the increase in stability of BANdel over BAN was "very surprising" and "significantly" and "substantially" greater than what would have been expected based on the combined teachings of Suzuki and Bisgaard-Frantzen. Borchert Decl. [App. 1430]; Amendment, dated Sept. 6, 2004, at 4-5 [App. 976-77].

However, once the expectations of a protein engineer of ordinary skill as of March 29, 1995 are defined, the results presented in the Borchert Declaration are neither surprising nor significantly or substantially greater than what a protein engineer of ordinary skill would have expected in view of the prior art.

By way of introduction, α-amylases are enzymes, that is, they are proteins that catalyze the breakdown of starch into simple sugars. Zeikus Decl. ¶ 20 [App. 558]. Proteins are essentially chains of amino acids that fold into three-dimensional structures. Zeikus Decl. ¶ 13 [App. 556-57]. The activity and stability of α-amylases depend on their three-dimensional structures, or the arrangement in space of an α-amylase's atoms. Zeikus Decl. ¶¶ 19, 25 [App. 557-58]. A protein's stability, *i.e.*, its ability to maintain its folded state, is in large part determined by how compactly and rigidly the protein folds: the more compact and rigid the folding, the greater its stability. Zeikus Decl. ¶ 26 [App. 558-59]. Within any protein are a number of "weak links" that render it susceptible to unfolding. Zeikus Decl. ¶ 35 [App. 561]. There are different classes of weak links; one class that was well known as of March 29, 1995 is a

flexible segment within a protein referred to as a "loop." Zeikus Decl. ¶¶ 19, 33 [App. 557-58, 560]. Shortening loops is one way of stabilizing proteins. Zeikus Decl. ¶ 33 [App. 560].

The three-dimensional structure, and thus activity and stability, of an α-amylase is notably dependent on the interactions between the amino acids within its protein chain, but is also influenced by extrinsic factors, such as heat and the presence or absence of calcium. Zeikus Decl. ¶¶ 21-24, 27 [App. 558, 559]. Heat lowers the stability of α-amylases by causing them to unfold, and the ability of an α-amylase to withstand heat is referred to as "thermostability" or "thermal stability." Zeikus Decl. ¶¶ 24, 27 [App. 558, 559]. In contrast to heat, calcium increases the stability of α-amylases. Zeikus Decl. ¶¶ 23, 37 [App. 558, 561].

BSG and BLA are thermozymes, which are enzymes that are active at high temperatures, whereas BAN is a mesozyme, which is an enzyme that is active under moderate temperatures. Zeikus Decl. ¶ 30 [App. 559]. In general, thermozymes are more rigid and compact than mesozymes, and have fewer weak links that cause their unfolding. Zeikus Decl. ¶¶ 31, 35 [App. 560, 561]. Because they have fewer weak links, thermozymes are less dependent on calcium for stability than mesozymes. Zeikus Decl. ¶ 38 [App. 561-62].

Knowing that BSG is a thermozyme and BAN is a mesozyme, one of ordinary skill in protein engineering as of March 29, 1995 would have expected that the removal of a given weak link would stabilize BSG to a substantially greater degree than removing that corresponding weak link in BAN. Zeikus Decl. ¶ 57 [App. 566]. This is because, despite the elimination of one weak link in BAN, one would have known that the enzyme still has a number of other weak links that make it susceptible to unfolding. Such remaining weak links offset the stabilizing effect of eliminating one weak link. *Id.* On the other hand, one would have expected that removal of one weak link in the otherwise stable thermozyme, BSG, results in an substantial enhancement of the stability of the enzyme, more so than is observed for the mesozyme BAN. *Id.*

The effect of introducing Suzuki's double deletion in BSG and BAN can be likened to plugging a hole -- thus removing a "weak link" -- in a leaky roof. In this analogy, the mesozyme BAN is akin to a leaky roof with 20 holes, whereas the thermozyme BSG is more akin to a leaky roof with two holes. Plugging one hole in the roof with two holes will yield a 50% improvement in the leakiness of that roof, while plugging only a single hole in the roof with 20 holes will only yield a 5% improvement in the leakiness of that roof. Overall, by this analogy, there would be a ten-fold relative improvement of the two-hole leaky roof as compared to the 20-hole leaky roof. Zeikus Decl. ¶ 58 [App. 566-67].

Thus, given the significantly fewer weak links in the thermozyme relative to the mesozyme, one of ordinary skill in protein engineering would have expected as of March 29, 1995 that shoring up a weak link would result in a substantially greater relative improvement in the thermostability of BSG under any experimental conditions. Zeikus Decl. ¶ 59 [App. 567].

The expected differential effect of introducing a stabilizing mutation into BSG vs. BAN is even further enhanced under the conditions employed in the Borchert Declaration. Zeikus Decl. ¶ 59 [App. 567]. Specifically, the calcium concentration used in the Borchert Declaration is one hundredth of that used in Suzuki, and one tenth of that used elsewhere in the prior art. Zeikus Decl. ¶ 60 [App. 567]. Under conditions of low calcium, BAN has an increased number of weak links and is thus destabilized. Zeikus Decl. ¶ 64 [App. 568]. On the other hand, BSG is not as reliant on calcium for stability, so the reduction in calcium will not significantly increase the number of its weak links. *Id.*

The result of the destabilization of BAN is that the apparent difference between the stability of BSG relative to BAN is enhanced. Zeikus Decl. ¶ 62 [App. 568]. In other words, the increased number of weak links in BAN as compared to BSG under conditions of low calcium concentration further masks the stabilizing effect of the two amino acid deletion in BAN, and thus further enhances the already-expected differential in the in improvement in stability of BSGdel vs. BSG relative to BANdel vs. BAN. Zeikus Decl. ¶ 64 [App. 568]. Under such conditions, a protein engineer of ordinary skill as of March 29,

1995 would not have been surprised that BSGdel exhibits an apparent relative improvement of 5.7-fold over BANdel. Zeikus Decl. ¶ 65 [App. 568-69].

Thus, the data in the Borchert Declaration are insufficient to rebut the *prima facie* obviousness based on Suzuki and Bisgaard-Frantzen that was properly found by the examiner.

4. Claims 1 And 3 Are Obvious Over The Machius Publication

a. Machius is prior art to the '031 patent

Machius, which was published by March 13, 1995,[32] is prior art to the '031 patent because the earliest effective filing date for claims 1 and 3 is after Machius published. *See* note 10, *supra*. Machius was not cited by the examiner or Novozymes during prosecution.

b. Machius describes the teachings of Suzuki and Bisgaard-Frantzen and provides the basis for one to expect that BSGdel will have a substantially increased thermostability relative to BANdel

Machius describes the three-dimensional structure of BLA, which was the first published three-dimentional structure of a *Bacillus* α-amylase. Zeikus Decl. Ex. 8 at 545 [App. 805]. Machius also analyzed the three-dimentional structure as it pertains to Suzuki's double deletion. Machius notes that the region in BLA corresponding to Suzuki's region I in BAN, *i.e.*, the region containing Arg-176 and Gly-177, "is a loop on the surface of domain B."[33] Zeikus Decl. ¶ 47 [App. 564]. It was well known by March 29, 1995 that loop regions render proteins particularly susceptible to unfolding (*i.e.*, are weak

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32 Machius *et al.*, *Crystal Structure of Calcium-depleted Bacillus licheniformis α-amylase at 2.2Å Resolution*, 246 J. MOL. BIOL. 545 (1995), including a copy of the cover page of the March 3, 1995 issue in which it appeared showing a March 13, 1995 date stamp of the University of Minnesota Bio-Medical Library (Zeikus Decl. Ex. 8) [App. 804-805].

33 Novozymes may attempt to dismiss the teachings of Machius on grounds that (i) the authors did not release the atomic coordinates until long after the effective date of the '031 patent, (ii) the crystal structure of Machius does not reflect the true three-dimensional structure of an α-amylase because it was based on a calcium-depleted enzyme or (iii) a second Machius paper published in 1998 presented a three-dimensional structure of an α-amylase under normal calcium conditions that was different from the structure of the Machius 1995 paper. None of those reasons, however, change the teachings of Machius that were available to a protein engineer of ordinary skill as of the effective filing date of the '031 patent. Moreover, because the loop of region I is a surface loop, its destabilizing effect is expected to be independent of calcium. Thus, the Machius 1998 paper does not alter the conclusions regarding the Machius 1995 paper. Zeikus Decl. at 12 n. 17 [App. 564].

links), and that thermozymes tend to have shortened loops relative to mesozymes as a means to increase their stability. Zeikus Decl. ¶ 48 [App. 564]. This was explicitly recognized by Machius, who noted that the loop of region I "is enlarged in [BAN] by two extra residues [as compared to BLA], which could cause increased mobility of this region and a decreased thermostability of the whole protein." *Id.* Thus, Machius provided a structural basis for the increased stability of BLA relative to BAN, that is, a shortening of a surface loop in BLA. *Id.*

Figure 7 of Machius is an amino acid sequence alignment of BAN, BLA and BSG and Machius predicted, based on the homology among them, that "the three-dimensional structures of [BAN and BSG] can be expected to be very similar to that of BLA." Zeikus Decl. ¶ 49 [App. 565].

Thus, Machius teaches over and above the teachings of Suzuki that (i) Suzuki's region I is within a surface loop that contains two additional amino acids in BAN and BSG relative to BLA; (ii) that the enlarged loop in BAA could cause "increased mobility of this region and a decreased thermostability of the whole protein;" and (iii) that the three-dimensional structures of BAN, BSG and BLA are expected to be similar. Zeikus Decl. ¶ 50 [App. 565]. Inventor Borchert admitted as much at his deposition. *See* Section V.B.2.b, below.

Thus, Machius presents in a *single* prior art reference all of the teachings of the two references that formed the basis of the examiner's *prima facie* obviousness case plus a compelling explanation of why the double-deletion made by Suzuki in BAN would be expected to result in an even more stable α-amylase if that very same double-deletion were made in BSG. This compelling obviousness, based on the protein engineer's Holy Grail -- the three-dimensional structure -- is not only stronger than the combination rejection raised by the examiner but is virtually unrebutable by any evidence of unexpected results, including the evidence of the Borchert Declaration (which, as discussed above, was not evidence of anything unexpected).

Where, as here, the prior art explicitly suggests the identical change that is the difference between the claimed invention and the prior art and the patentee has not shown significantly unexpected results in

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light of the prior art, the "invention" is properly held obvious. *See In re Eli Lilly*, 902 F.2d at 947-48; *In re Nolan*, 553 F.2d at 1266-67. Moreover, because Machius was not cited by the examiner or Novozymes during prosecution, there is no reason to defer to the examiner's patentability finding when an allegation of invalidity is based on a reference that was not considered during prosecution. *See American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984).

For these reasons, claims 1 and 3 are obvious over Machius. And, for these reasons, yet another substantial question about the '031 patent requires that Novozymes' motion be denied.

B. The '031 Patent is Unenforceable Because Novozymes Engaged in Inequitable Conduct and Committed Prosecution Laches

The '031 patent resulted from Novozymes' inequitable conduct, and is unenforceable. There is no dispute that inventor Borchert was "familiar" with Machius, which predates the effective filing date of the claims at issue, and that Machius was not disclosed to the Patent Office. As shown below, Machius was highly material to the '031 patent, as it taught beyond the Suzuki reference and made clear the "surprising results" were not surprising at all. Against the backdrop of Novozymes' desperate effort to get a patent "on" SPEZYME® Ethyl, a finding of deceptive intent is easily made.

1. Legal Standard For Inequitable Conduct

Patent applicants and their attorneys must prosecute patent applications in the Patent Office with candor, good faith, and honesty. *See Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). A breach of this duty may result in inequitable conduct. *See id.* A court may find inequitable conduct based on the failure to disclose material information if there is clear and convincing evidence that: (1) the omitted prior art was material; (2) the applicant knew of the prior art and its materiality and (3) the applicant failed to disclose the prior art with an intent to mislead the Patent Office. *See Elk Corp.*, 168 F.3d at 30; *Molins*, 48 F.3d at 1178. "The more material the omission or misrepresentation, the lower the level of intent required to establish inequitable conduct, and vice versa." *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1256 (Fed. Cir. 1997). *See also Elk Corp.*, 168 F.3d at 32.

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Information is material when it is not cumulative to information already of record in the application and it either establishes a *prima facie* case of unpatentability of a claim (alone or in combination with other information) or refutes or is inconsistent with a position taken by the applicant in opposing the examiner's argument of patentability. *See* 37 CFR § 1.56(b); *Elk Corp.*, 168 F.3d at 31; *Critikon*, 120 F.3d at 1258 (finding that withheld prior art was material since it showed two features of the claims that the examiner found to impart novelty).

A party's intent to mislead or deceive the Patent Office is rarely established by direct evidence; it is generally inferred from the facts and circumstances surrounding the applicant's overall conduct. *See Elk Corp.*, 168 F.3d at 32; *Molins*, 48 F.3d at 1180-81. The Federal Circuit has held that lower courts can infer intent when a patent applicant knows, or should have known, that withheld information would be material to the Patent Offices' consideration of a patent application. *See Critikon*, 120 F.3d at 1256 (finding an intent to deceive because the applicant's patent attorney had reviewed the withheld prior art reference in detail and was aware that this reference described features of the claims that the examiner had considered to be novel).

2. Novozymes Failed To Disclose Machius, Which Was More Material To Patentability Than The Art Considered By The Examiner

What Novozymes concealed from the examiner in Machius was the first public disclosure of the three-dimensional structure of a *Bacillus* α-amylase. Based on that structure, Machius explained why the double-deletion mutation made by Suzuki in BAA would, if made in BSG, be expected to substantially increase its thermostability. Machius presents a far stronger case of *prima facie* obviousness than the combination of Suzuki and Bisgaard-Frantzen.

a. The two references cited by the examiner do not disclose what Machius taught

The Suzuki authors did not have available to them the three-dimensional structure of either BAN or BLA, and therefore did not recognize that region I fell within a loop on the surface of BAN. Zeikus Decl. ¶ 44 [App. 563]. Other than speculating that the deletion improves thermostability through changes

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in charge, hydrophobicity or size of amino acid side chains, Suzuki did not provide the structural basis for the importance of region I of BAN for enzyme stability. *Id.* Thus, Suzuki did not provide a scientific basis for the observed increase in the thermostability in the BANdel relative to BAN. *Id.*

Specifically, Machius explains that: (i) Suzuki's region I is within a surface loop that contains two additional amino acids in BAN and BSG relative to BLA; (ii) the enlarged loop in BAA could cause "increased mobility of this region and a decreased thermostability of the whole protein"; and (iii) the three-dimensional structures of BAN, BSG and BLA are expected to be similar. Zeikus Decl. ¶ 50 [App. 565]. None of this information was described by Suzuki or Bisgaard-Frantzen.

This additional information found in Machius was far more relevant to patentability than the combined disclosures of Suzuki and Bisgaard-Frantzen and is, therefore, more material than these two references cited by the examiner and non-cumulative to those references.

b. Novozymes' inventor, Dr. Borchert, **REDACTED**

Novozymes' inventor, Dr. Borchert, **REDACTED**

Specifically, Dr. Borchert

REDACTED

Finally, Dr. Borchert

REDACTED

c. Dr. Borchert was thoroughly familiar with Machius when he participated in an interview with the examiner

Dr. Borchert testified that **REDACTED**

Borchert Tr. 158:6-7 [App. 933]. Even more significantly, on August 27, 2004, just one week before he

participated in an interview (on September 3, 2004) with the examiner in the '031 patent prosecution (Borchert Dep. Ex. 51, Tab F [App. 971-72]; Borchert Tr. 150:19-151:2 [App. 930-31]), Dr. Borchert executed a declaration in a patent interference between Novozymes and Genencor involving α-amylase mutants. Borchert Dep. Ex. 58 [App. 1304-32]; Borchert Tr. 148:17-19 [App. 928]. Several paragraphs of that interference declaration discussed the teachings of Machius (Borchert Tr. 148:21-150:14 [App. 928-30]) and, just one month later (on September 27, 2004), Dr. Borchert was cross-examined on his statements in the interference declaration concerning the Machius paper. Borchert Dep. Ex. 59 [App. 1333-1413]; Borchert Tr. 151:13-152:12 [App. 931-32]. Clearly, Dr. Borchert was thoroughly familiar with the details of Machius during prosecution of the '031 patent and had carefully reviewed Machius the same week he interviewed the examiner and within the month thereafter when he was deposed. Therefore, he knew, or should have known, that Machius presented compelling new evidence that was highly material to obviousness but was not before the examiner in either Suzuki or Bisgaard-Frantzen.

3. Novozymes Committed Inequitable Conduct

Notwithstanding Dr. Borchert's understanding of the materiality of Machius, Novozymes intentionally withheld Machius from the examiner in a misguided, desperate attempt to obtain a patent that would exclude Genencor's SPEZYME® Ethyl protein from the market. Genencor's successful launch of SPEZYME® Ethyl in April 2004 threatened Novozymes' established, profitable α-amylase products. As a result, Novozymes feverishly formulated a concerted strategy to respond to this serious new competitive threat, featuring a heavy emphasis on obtaining patent protection preventing sales of SPEZYME® Ethyl. NV-0104995 [App. 2294].

As part of this strategy, Novozymes obtained a SPEZYME® Ethyl sample from Genencor customers and embarked on a crash project to determine the amino acid sequence of the protein. NV-0105470 [App. 2293]; NV-0105106-7 [App. 2290-91]; Borchert Dep. Ex. 51, Tab E [App. 970]. During all of this activity, Dr. Borchert remained informed of Novozymes' progress towards sequencing SPEZYME® Ethyl. C. Jorgenson Dep. Ex. 6 [App. 1474-77], S. Jorgenson Dep. Ex. 8 [App. 1459-60],

Borchert Dep. Ex. 51 [App. 970]. After determining a nearly complete amino acid sequence of SPEZYME® Ethyl by August 15, 2004, Novozymes placed top priority on obtaining a patent that would cover Genencor's product. NV-0104995 [App. 2294].

Dr. Borchert played a key role in Novozymes' efforts to obtain such a patent. Specifically, Dr. Borchert provided a declaration purporting to show unexpected results for BSG α-amylases having a deletion at amino acids 179 and 180. Arnold Dep. Ex. 43 [App. 1426-43]. Further, Dr. Borchert participated in an interview with the examiner for the '031 patent where the examiner indicated that she would allow the claims of the '031 patent based on Dr. Borchert's Declaration. Borchert Dep. Ex. 51, Tab F [App. 971-72]. As such, Dr. Borchert was intimately familiar with both the claims of the '031 patent and the highly material Machius reference, much like the culpable patent attorneys of *Critikon*. *See Critikon*, 120 F.3d at 1256.

Dr. Borchert also knew, or should have known, that the results presented in his declaration were expected by one of ordinary skill in protein engineering who was aware of the teachings of Machius. Further, Dr. Borchert knew that the examiner decided to allow the '031 patent's claims based solely on the allegedly unexpected results in his declaration. Borchert Dep. Ex. 51, Tab F [App. 971-72]. Nonetheless, Dr. Borchert failed to present Machius for the examiner to consider, just as the culpable patent attorneys of *Critikon* failed to present a reference that taught the element acknowledged by the examiner to be the point of novelty. As such, like the court in *Critikon*, this Court should infer from this clear and convincing evidence that Dr. Borchert intended to deceive the Patent Office when he failed to submit Machius for consideration of its effect on the patentability of the '031 patent's claims.

4. The '031 Patent is Unenforceable Because of Prosecution Laches

Novozymes egregious conduct in prosecuting the claims that ultimately issued in the '031 patent should bar it from enforcing the '031 patent against Genencor and EDC. Under the doctrine of prosecution laches, a patent applicant's unreasonable and unexplained delay in prosecuting patent claims can bar enforcement of the claims, even if the applicant technically complied with relevant patent statutes

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and rules. *See Symbol Techs., Inc. v. Lemelson Med. Educ. & Research Found.*, No. 04-1451, 2005 WL 2173572, at *6 (Fed. Cir. Sept. 9, 2005).

Novozymes waited until September 9, 2004, more than eight years, before it presented the claims that ultimately issued as the '031 patent. Nothing in the '031 patent prosecution history can explain this delay.[34]

In fact, until the summer of 2004, Novozymes **REDACTED** on convincing the Patent Office to issue the claims of the '031 patent. Borchert Tr. 32:3-34:4 [App. 913-14]. What changed? Novozymes recognized the competitive threat posed by SPEZYME® Ethyl and learned that SPEZYME® Ethyl contained the Suzuki double-deletion; Novozymes then suddenly became very interested in obtaining allowance of claims to assert against SPEZYME® Ethyl, as discussed above. Borchert Tr. 34:5-24 [App. 914]; NV-0081594 [App. 2272].

The egregiousness of Novozymes' conduct is aggravated because its targeted and delayed prosecution of the '031 patent unfairly prejudiced both Genencor and EDC. Genencor had carefully assessed the scope of Novozymes' existing patent claims and the state of the prior art when developing SPEZYME® Ethyl, concluding that none of Novozymes' claims in force in 2003 would read on SPEZYME® Ethyl, and, further, that Suzuki was likely to prevent Novozymes from issuing such a patent claim. Crabb Decl. ¶ 16 [App. 1484-85]. To allow Novozymes to enforce the '031 patent's claims now would allow Novozymes to benefit from laying in the weeds, and would be unfair to Genencor's customers, who chose SPEZYME® Ethyl over Novozymes' product on the merits of the products and for many other reasons (*see* Sections VI.A, B, below).

Prosecution laches should bar Novozymes from enforcing the '031 patent.

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[34] In fact, while Novozymes presented claims superficially similar to the '031 patent's issued claims in the '648 application as filed in that both sets of claims recited the Suzuki double deletion, these claims never substantially advanced through prosecution. Indeed, when faced with an obviousness rejection over Suzuki, Novozymes substantially narrowed the scope of the as-filed claims in a manner plainly excluding SPEZYME® Ethyl.

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VI. THE COURT SHOULD NOT EXERCISE ITS EQUITABLE POWER TO GRANT AN INJUNCTION

A. Novozymes Will Not Be Irreparably Harmed Without an Injunction

The Federal Circuit is clear that its "case law and logic both require that a movant cannot be granted a preliminary injunction unless it establishes *both* of the first two [preliminary injunction] factors, *i.e.*, likelihood of success on the merits and irreparable harm." *Amazon.com*, 239 F.3d at 1350 (citing *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 141 F.3d 1084, 1088 (Fed. Cir. 1998)). *See also National Steel Car*, 357 F.3d at 1325. Further, while a "strong showing of likelihood of success on the merits coupled with continuing infringement" does raise a presumption of irreparable harm to the patentee, *Reebok*, 32 F.3d at 1555-56; *Eli Lilly & Co. v. American Cyanamid Co.*, 82 F.3d 1568, 1578 (Fed. Cir. 1996); *Chrysler Motors Corp. v. Auto Body Panels of Ohio, Inc.*, 908 F.2d 951, 954 (Fed. Cir. 1990), this presumption does not "necessarily or automatically override the evidence of record. It is rebuttable." *Reebok*, 32 F.3d at 1556 (citing *Rosemount, Inc. v. U.S. Int'l Trade Comm'n*, 910 F.2d 819, 822 (Fed. Cir. 1990)).

As shown above, Novozymes has plainly failed to make a strong showing on the issues of infringement and validity, and therefore is not entitled to a presumption of irreparable harm. Just as importantly, it is clear that any harm Novozymes suffered is neither "irreparable," nor is it attributable to alleged patent infringement.

1. Novozymes Alleged Damages Are Quantifiable

The basic elements of Novozymes' claimed "irreparable harm" are alterations in relevant market conditions, namely, lost sales, price erosion and lost convoyed sales. These factors, however, are standard elements of a lost profits/damages analysis, and there are well-established methodologies that economists employ to quantify these types of harms. *See* Declaration of David J. Teece ("Teece Decl.") ¶¶ 17-22 [App. 1854-55]. Novozymes simply asserts that "loss of market share and corresponding price erosion, translates into a significant, immeasurable, and non-compensable loss," but fails to provide any supporting evidence. (PI Mot. 35.) Moreover, its own statements clearly contradict this claim.

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Novozymes' Greg LeFebvre quantified the lost market share

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and price erosion

in his declaration and at his deposition, and Novozymes makes similar statements throughout its brief. Declaration of Gregory LeFebvre in Support of Novozymes' Motion for Preliminary Injunction ("LeFebvre PI Decl.") ¶ 14 and Deposition of Gregory LeFebvre ("LeFebvre Tr.") 109-112 [App. 1639-42]. In fact, Mr. LeFebvre **REDACTED** LeFebvre Tr. 130-134 [App. 1660-64]. Moreover, the relevant fuel ethanol alpha-amylase market is currently just a two-player market – Genencor and Novozymes – making the task of calculating lost profits that much easier. Beto Decl. ¶ 5 [App. 1514], Nelson Decl. ¶ 5 [App. 1497], LeFebvre Tr. 39-40 [App. 1569-70]. *See also Eli Lilly*, 82 F.3d at 1578 (finding it easy to calculate lost profits in the context of a discrete, five-player market).

2. Novozymes Alleged Harm Is Not "Irreparable"

A harm is only "irreparable" if a court is unable to remedy it even if the plaintiff prevails in a final adjudication. *See Freedom Holdings, Inc. v. Spitzer*, 408 F.3d 112, 114 (2d Cir. 2005) (stating "[t]o satisfy the irreparable harm requirement, Plaintiffs must demonstrate that absent a preliminary injunction they will suffer an injury that is neither remote nor speculative, but actual and imminent, and one that cannot be remedied if a court waits until the end of trial to resolve the harm") (quotation omitted); 13 James Wm. Moore, MOORE'S FEDERAL PRACTICE § 65.06[2] (3d ed. 2005).

The two-player competitive landscape also belies Novozymes' argument that market conditions will be irreversibly (or "irreparably") altered absent a preliminary injunction. Simply stated, customers who currently purchase α-amylase enzymes for dry grind fuel ethanol production choose SPEZYME® Ethyl or Liquozyme SC to meet their liquefaction needs. If SPEZYME® Ethyl is removed from the market, customers will logically turn to Liquozyme SC. In fact, Mr. LeFebvre admitted that alleged customer losses were not "irreversible." LeFebvre Tr. 61 [App. 1591].

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3. Novozymes' Alleged Harm Is Not Attributable To Alleged Patent Infringement

Further, the loss in market share, lost customers and price erosion of which Novozymes complains largely occurred prior to any alleged infringement of the '031 patent. LeFebvre Tr. 117 [App. 1647]. Genencor began selling SPEZYME® Ethyl in April 2004. Beto Decl. ¶ 3, Ex. 1 [App. 1514, 1517-28]. Novozymes' '031 patent did not issue until March 15, 2005, approximately eleven months later. Harm that occurred in that timeframe is simply not recoverable because infringement at that time was a legal impossibility. And Novozymes provides no basis for believing that there is any "*irreversible* alteration of market conditions" that will take place in the future if the preliminary injunction is not granted, *above and beyond* the "alteration" that has *already* taken place before the '031 patent issued. Teece Decl. ¶¶ 25-28 [App. 1856-57].

This is also true with regard to the alleged harm to reputation or good will. Teece Decl. ¶¶ 29-33 [App. 1857-58]. In its brief, Novozymes fails to offer any specific examples of reputation harm that it suffered post-patent issuance. Rather, it simply contends that "resentment is building among its customers because of what is now perceived as over-pricing by Novozymes," and that, without a preliminary injunction, "it will be very difficult to return the market to pre-infringement conditions where Novozymes enjoyed a good reputation as a reliable industrial enzyme supplier in general, and a reliable alpha-amylase industrial enzyme supplier in particular." (PI Mot. 2-3, 33.)

Of course, Novozymes has not proffered any evidence to support the premise that that it had a good reputation to begin with. In fact, there are documents in the record to the contrary. LeFebvre Dep. Ex. 28 [App. 1738-39]

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Moreover, there is nothing in the record to support the premise that Genencor's actions have tainted specifically Novozymes' reputation.[35] LeFebvre Dep. Ex. 29).

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[35] Novozymes argues that Genencor's act of offering SPEZYME® Ethyl at a price lower than Novozymes offers Liquozyme SC harms Novozymes reputation and good will. This implies that the only reason customers purchase SPEZYME® Ethyl over Liquozyme SC is price, which is untrue. When considering which alpha-amylase product to purchase, customers also consider product performance, technical support, customer service, long term availability of the product,

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(emphasis added) [App. 1741]. And, Novozymes links its reputation harm with the introduction of SPEZYME® Ethyl and its subsequent price reductions for Liquozyme SC. These acts, however, occurred well before the '031 patent issued. Novozymes is simply not entitled to a remedy for alleged harm that occurred prior to March 15, 2005.

Novozymes' argument that it has been irreparably harmed because of lost convoyed sales also lacks factual support. Fuel ethanol producers who use α-amylase enzyme products for liquefaction of corn starch often use glucoamylase enzyme products for a subsequent step in fuel ethanol production, called "saccharification." Beto Decl. ¶ 8 [App. 1515]; Nelson Decl. ¶ 7 [App. 1497]. Genencor competes in this market with its G-ZYME 480 product, while Novozymes' has its Spirizyme Fuel product. Beto Decl. ¶ 8 [App. 1515]. Customers who purchase one company's α-amylase product do not need to purchase their respective glucoamylase product, thus a sale of one product (glucoamylase or α-amylase) simply does not guarantee sales of the other product. *Id.* at ¶ 9 [App. 1515]; Nelson Decl. ¶ 7 [App. 1497]. Moreover, Novozymes

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LeFebvre Tr. 48, Exs. 30 and 31 [App. 1578, 1744-50].

Novozymes simply has not been and will not be irreparably harmed, *sans* injunction.

B. The Public Interest Will Be Harmed If The Court Orders SPEZYME® Ethyl Off The Market

The Court should also consider the impact issuing a preliminary injunction will have on the public interest. Typically in patent infringement cases, "the focus of the district court's public interest analysis should be whether there exists some critical public interest that would be injured by the grant of

(continued...)

prior relationships and loyalty, payment options and sales tactics. Beto Decl. ¶ 6, Ex. 2 [App. 1514-15, 1529-30]; Nelson Decl. ¶ 6 [App. 1497]; Teece Decl. Exs. 14, 24-26 [App. 2138-46, 2253-68]; LeFebvre Dep. Exs. 27-29 [App. 1735-43].

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preliminary relief." *Hybritech*, 849 F.2d at 1458. Such an interest exists here, and would be injured if SPEZYME® Ethyl is taken off the market before a final determination of the merits of this case.

The fuel ethanol industry "provides a significant contribution to the American economy," both in economic and environmental terms. Teece Decl. Ex. 12 [App. 2114-33]. Total ethanol production for 2005 is estimated at an all time high of 3.9 billion gallons on a year-end capacity base of 4.3 billion gallons. *Id.* This unprecedented demand is spurred by record oil and gasoline prices, federal and state clean fuel programs, and mounting concerns about the U.S.'s growing dependence on imported energy. Teece Decl. Ex. 13 [App. 2134-37].

If SPEZYME® Ethyl is forced off of the market, Novozymes has a strong economic incentive to raise the price of Liquozyme SC, which would adversely impact price competition in the market. Teece Decl. ¶¶ 42-43 [App. 1859-60]. In fact, this has been Novozymes' intent all along. Teece Decl. ¶ 42 [App. 1859], Exs. 18, 21-23 [App. 2171-85, 2233-52]; LeFebvre Tr. 159-160, 186-188

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[App. 1689-90; 1716-18].

Enjoining sales of Genencor's SPEZYME® Ethyl product would also deprive customers a choice of suppliers (and better product and service performance) that would otherwise be available to them. As a general matter, economists believe that the "public interest" is served by enhancing the range of choices available to consumers. Teece Decl. ¶¶ 44-46 [App. 1860]. Many customers purchase SPEZYME® Ethyl because they believe that it has superior product performance and that Genencor provides excellent customer service and technical support.

Novozymes' claim that the public interest of the people in Franklinton, North Carolina (i.e., the location of its U.S. plant) will be harmed absent the issuance of a preliminary injunction is entirely unsupported. Novozymes' complains that if there is no injunction, it will have to shutter the Franklinton plant. Yet, when Novozymes' declarant, Mr. LeFebvre testified almost a year and a half after

SPEZYME® Ethyl came on the market, he simply could not support that hysterical claim. LeFebvre Tr. 149:19-151:3 [App. 1679-81].[36]

C. The "Balance of Hardships" Tips Heavily In Favor Of Genencor and EDC

Finally, when considering whether to issue a preliminary injunction, a court must also "balance the harm that will occur to the moving party from the denial of the preliminary injunction with the harm that the non-moving party will incur if the injunction is granted." *Hybritech*, 849 F.2d at 1457. There is an important asymmetry that the Court should consider here. If Genencor and EDC are preliminarily enjoined when they should have been allowed to participate in the market (*i.e.*, because they are later found not to be liable for patent infringement), they will lose sales and profits for which they will likely never be fully compensated. By contrast, if Novozymes is denied an injunction when it should have been granted, then Novozymes will still be able to obtain compensation for the harm that it suffered in the form of money damages for lost profits on lost sales, price erosion damages, etc., as explained above. Teece Decl. ¶¶ 34-37 [App. 1858].

Further, EDC will suffer particular harm if this Court issues a preliminary injunction. EDC simply distributes SPEZYME® Ethyl for Genencor. EDC does not manufacture SPEZYME® Ethyl, nor was EDC involved in its development. Nelson Decl. ¶ 9 [App. 1498]. It would be manifestly unfair to preclude EDC from selling SPEZYME® Ethyl before a full hearing on the merits, particularly when any actionable harm caused by EDC between before the conclusion of the litigation would be fully compensable through money damages.

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[36] Novozymes' public interest argument also myopically assumes that the interests of "its" Franklinton community should be preferred to those of Beloit, WI, where SPEZYME® Ethyl is made. Teece Decl. ¶¶ 48-50 [App. 1861-62].

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VII. CONCLUSION

The Court should decline Novozymes' invitation to substitute the Court's equitable powers for fair competition in the market. Genencor and EDC respectfully request that the Court deny Novozymes' motion for preliminary injunction.

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CERTIFICATE OF SERVICE

I, Donald E. Reid, hereby certify that on the 23rd day of September, 2005 a copy of the Public Version of Genencor's And EDC's Brief In Opposition To Novozymes' Motion For Preliminary Injunction was served by electronic filing on the following counsel of record.

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